ORIGINAL RESEARCH

Timely Respiratory Support Can Improve Clinical Outcomes of Premature Infants in a Country with Limited Medical Resources due to Chronic Conflicts

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Abstract

Introduction: The children of Iraq have suffered greatly from military conflicts and economic sanctions since 1991. Recent years have shown some improvement in neonatal and infant mortality but more efforts are needed; prematurity and associated respiratory distress syndrome (RDS) remain the two leading causes. In this study, we investigated the efficiency of timely institution of nasal continuous positive airway pressure (nCPAP) in stabilizing these infants. These data are needed for the optimum allocation of financial resources to improve the healthcare outcomes of infants.

Patients and methods: This prospective cross-sectional study was carried out over 6 months from April 1st to September 30th, 2022. Inborn preterm infants born between 26 and 32^{+0} weeks' gestation who required respiratory support after delivery or immediately after admission were included. The data for the initial course of respiratory support and outcomes were assessed.

Results: In our cohort of 123 infants, nCPAP significantly increased the likelihood of clinical stabilization in infants with a gestational age (GA) >28 weeks ($p = 0.022$), birth weight (BW) ≥1500 gm ($p = 0.016$), use of antenatal steroids ($p = 0.002$), Apgar score at 5 minutes of life ($p = 0.022$), mild radiographic findings ($p = 0.007$), and sepsis without prolonged rupture of membranes ($p = 0.027$). Nasal continuous positive airway pressure also reduced the need for surfactant ($p = 0.001$) and mortality ($p = 0.0001$).

Conclusion: Early institution of nCPAP improved the respiratory status of premature infants who were born at a gestational age from >28 to ≤32 weeks, had birth weight ≥1500 gm, had received antenatal steroids, had a 5-minute Apgar score >7, and had sepsis but no PROM. The success of early nCPAP reduced the need for surfactant and mechanical ventilation, and the risk of pulmonary hemorrhage and mortality.

Keywords: Baby, Infant, INSURE, Mechanical ventilation, Minimal invasive surfactant therapy, Neonatology, Neonate, Neonatal intensive care unit, Newborn, Preterm infants, Respiratory distress syndrome.

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Introduction

Iraq is a middle-income country with a total population of 44.5 million. A large proportion of this community is relatively young; 20 million (45%) are under the age of 15 years (y) and 3.9 million (17%) are <5 years. There are 1.2 million annual births, and as in any other country, children are a relatively high-risk section of its population. The children here suffered considerably during the Gulf War of 1991 and its aftermath.[1–4] An estimated 46,000 Iraqi children were killed during the wars beginning in 1991, and many more were lost in subsequent conflicts and economic sanctions; the negative healthcare sequelae of these conflicts can still be seen after two decades.[1,5,6]

In a panoramic view, Iraq is a country with moderately-high neonatal and childhood mortality. Notably, 58% of all <5 year deaths occur in neonates.[7] In the 1980s, the average perinatal mortality rate (PMR) in Iraq was about 28 per 1,000 live births. However, following the onset of military conflicts during the 1990–1999 decade, the average PMR rose to 107 per 1,000 live births. The most important causes of neonatal deaths include prematurity (9.1% of all births) and its complications related to pulmonary immaturity and infections (47% of all neonatal deaths), birth asphyxia (20%), and congenital anomalies (17%).

Recent years have shown improved social safety and there has been some slow improvement in healthcare outcomes. During the period 1990–2020, the neonatal mortality has decreased from 26 to about 15/1,000 live births, and the infant mortality rate from 42 to 21.[8] The most frequently noted causes of neonatal deaths are still low birth weight, prematurity, perinatal infections, and birth asphyxia.[9] Children, per international conventions, ought to be

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protected from social adversities during armed conflicts but the efforts have not quite sufficed. Recent data show that despite all improvements, only 26.9% of all deliveries are currently attended by skilled birth attendants.[10]

In premature infants, respiratory distress syndrome (RDS) is the leading cause of morbidity and mortality in this region. Due to limitations in resources, we have stressed preventive and pre-emptive treatment such as with timely application of nasal-continuous positive airway pressure (nCPAP). If the work of breathing is high and there is an increasing need for oxygen, surfactant is administered as soon as possible.[11] Prenatally, a single course of corticosteroids is offered to women at risk of preterm delivery if they complete <34 weeks' gestation when pregnancy begins to be considered potentially viable. This treatment is administered ideally at least 24 hours (h) prior to delivery. This dose of corticosteroids improves survival and reduces the risk of RDS, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH).[11,12]

According to the European Consensus Guidelines, all spontaneously-breathing preterm infants with RDS should have access to CPAP for clinical management.[11] Intubation should be reserved for babies not responding to positive pressure ventilation via face masks or nasal prongs.[13] Surfactant therapy improves survival and reduces pneumothoraces, and therefore, is an important part of the management of RDS. Early initiation of CPAP may help prevent the harmful effects of intubation and mechanical ventilation (MV) during the transitional phase. The INtube, SURfactant, Extubate (IN-SUR-E) technique, involving surfactant bolus administration followed by brief bag ventilation and rapid extubation without ongoing ventilation, may also reduce lung injury.[14] Currently, the best-accepted method is using the less invasive surfactant administration (LISA) or minimally invasive surfactant technique (MIST).[15,16] If these modalities do not succeed, MV is used cautiously as a rescue modality to achieve "acceptable" alveolar function and prevent acidosis.[15] A previous Iraqi study at our center in 2013 showed a high failure rate of CPAP. In a cohort of 70 neonates, 37 (52.9%) failed CPAP, and 29 (78.3%) had to be rescued using MV.[17] In the present study, we re-assessed the impact of nCPAP as the initial modality for respiratory support and assessed the clinical outcomes in preterm infants born at a gestational age (GA) between 26 and 32^{+0} weeks. These data are important to optimize the allocation of financial resources to improve infant healthcare outcomes in an underserved area with longstanding conflicts and limited resources.

Patients and Methods

This single-center, prospective, cross-sectional study included 123 preterm (26–32 weeks' gestation) over 6 months (April 1, 2022–September 30, 2022) in the level 3 neonatal intensive care unit (NICU) of Baghdad Teaching Hospital/Medical City complex. This NICU is equipped with 20 incubators (Dräger and Atom), 22 monitors, 15 CPAP (SLE1000), and (medin CNO), which involve all modes of noninvasive ventilation (CPAP, nasal high-frequency oscillatory ventilation, nasal intermittent positive pressure ventilation, and synchronized nasal intermittent positive pressure ventilation). In addition, there are 9 ventilators SLE (4000, 5000) with the 3 main modes of ventilation (synchronized intermittent mandatory ventilation, assist/control ventilation, and pressure support ventilation). The unit has ready access to a blood gas analysis machine.

The inclusion criteria were: (A) GA of 26–32^{+0} weeks; (B) RDS, with at least two of the following findings: Tachypnea (respiratory rate >60/min), dyspnea (increased respiratory effort with nasal flaring expiratory grunting, and intercostal retractions); (C) need of supplementary oxygen; and (D) need of surfactant administration.[18,19] Exclusion criteria were birth defects affecting the respiratory system or other major congenital anomalies.

Data collected retrospectively from the records were: age, sex, GA, birth weight (BW), mode of delivery, being small for GA (BW <10th centile), maternal history of hypertension, diabetes mellitus, preeclampsia, prolonged rupture of membranes (PROM) >18 hours, antenatal steroids use, Apgar score at 1 and 5 minutes, intubation in the delivery room, use of CPAP as initial respiratory support, need for MV as initial respiratory support, use of surfactant, radiographic features of RDS, length of hospital stay (LOS), and caffeine supplementation.

Short-term outcomes included a change from CPAP to MV, pneumothorax, pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), sepsis, successful management with initial CPAP without a need to change to MV, and death. GA was calculated based on the mothers last menstrual period and/or either an early pregnancy ultrasound scan or a New Ballard score. The babies were initially treated with CPAP (5–7 cm H_2O) and FiO_2 of 0.3. Exogenous surfactant was administered through an endotracheal tube applying the INSURE technique. Indications for surfactant include preterm with RDS who fail nCPAP and require intubation and MV. Surfactant therapy was administered to infants who required FiO_2 >0.3–0.4 to maintain SpO_2 >90 percent despite the use of nCPAP or X-ray showing severe RDS (white lung) and if a preterm baby <30 weeks required intubation for stabilization. LISA use was not documented in any of the neonatal care units in Iraq. Based on radiological findings, the severity of RDS was graded as mild (mild granularity of lungs), moderate (generalized granularity of lungs with air bronchogram with preserved cardiac borders), and severe (opaque 'white-out' lungs with loss of cardiac borders).[20]

Continuous positive airway pressure failure was defined as the need for MV during the 1st week for ≥1 of the following indications: (A) no spontaneous breathing or frequent apnea; (B) marked retractions and/or respiratory rates ≥90 per minute; and (C) FiO_2 >0.4 to maintain a target SpO_2 of 90–94%.[21]

Statistics

Statistical analysis of data was carried out using the software package [Statistical Packages for Social Sciences (SPSS)], version 28. Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of the difference of different percentages (qualitative data) was tested using the Pearson Chi-square test with the application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the p-value was ≤ 0.05.[22–25]

Ethics

Patients were included after verbal parental consent. The identity of patients was kept anonymous. The ethical committees at the Children's Welfare Teaching Hospital and Baghdad Teaching hospital, Medical City approved the studies.

Results

123 preterm babies were included. The mean (± standard deviation, SD) of GA was 29.8 ± 1.6 weeks. Eleven (8.9%) had a GA <28 weeks and 112 (91.1%) were born between 28 and 32 weeks. Eighty (65.0%) were males. The mean BW was 1247.5 ± 291.8 gm; 38 (30.9%)

Table 1: Association between demographic characteristics and outcome of early CPAP (*n* = 103)

	CPAP prognosis (n = 103)				
	Failure n = 38		*Success n = 65*		
	No	*%*	*No*	*%*	*p-value*
Gestational age (weeks)					
<28 weeks	7	18.4	3	4.6	0.022*
28–32 weeks	31	81.6	62	95.4	
Mean ± SD	29.5 ± 1.9		30.3 ± 1.4		
Sex					
Female	11	28.9	21	32.3	0.722
Male	27	71.1	44	67.7	
Birth weight (gms)					
<1000 gm	8	21.1	3	4.6	0.016*
1000–1500 gm	21	55.3	35	53.8	
>1500 gm	9	23.7	27	41.5	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at <0.05 level

weighed ≥1500 gm, 67 (54.5%) between 1000 and 1500 gm, and 18 (14.6%) weighed <1000 gm. One hundred and two (82.9%) neonates were delivered by emergency cesarean sections, whereas 21 (17.1%) were delivered by normal vaginal deliveries. Fourteen (11.4%) cases were SGA. Ninety-four (76.4%) mothers received 1 course of antenatal steroids. The frequency of the need for respiratory support vis-à-vis the incidence of maternal risk factors was maternal hypertension (42, 34.1%), diabetes (14, 11.4%), preeclampsia (6, 4.9%), and prolonged (>18 hours) rupture of membranes (36, 29.3%).

At 1 minute, 117 infants (95.1%) had an Apgar score of <7 and 6 (4.9%) had ≥7. At 5 minutes, 23 (18.7%) had Apgar <7, and 100 (81.3%) had ≥ 7. Thirty (24.4%) were intubated in the delivery room, 103 (83.7%) were treated with early CPAP, and 20 (16.3%) needed early rescue MV. Thirty-five (28.5%) received surfactant and 101 (82.1%) were started on caffeine. Eighty-eight (71.5%) had radiographic changes of mild RDS, 12 (9.8%) had moderate, and 23 (18.7%) had severe changes. The mean LOS was 10.3 ± 6.8 (range 1–32) days. Twenty-seven (22%) stayed for ≤7 days, 67 (54.5%) for 8–14, 16 (13%) for 15–20, and 13 (10.6%) for >20 days.

Thirty-eight (30.8%) infants needed rescue MV after failure of CPAP. Twenty-six (21.1%) developed pulmonary hemorrhage, 6 (4.9%) had pneumothorax, 35 (28.5%) had sepsis, and 2 (1.6%), developed BPD. Twenty-three (18.7%) were referred to a tertiary pediatric referral hospital to continue treatment or failure to thrive.

Overall, 80 (65%) infants survived, and 43 (35%) died. One hundred and three (83.7%) infants received early CPAP but 38 (30.8%) had to be changed to MV. There were significant associations between GA ($p = 0.022$), BW ($p = 0.016$), and outcome of early CPAP, however, there was no significant association between gender ($p = 0.722$) and outcome of early CPAP. The outcome of early CPAP showed significant associations with the use of antenatal steroids ($p = 0.002$) and Apgar score at 5 minutes ($p = 0.022$). There was a higher risk of failure of CPAP if there was sepsis with prolonged (>18 hours) rupture of membranes ($p = 0.019$). There were no associations with maternal history (hypertension, diabetes, and preeclampsia), the mode of delivery ($p = 0.113$), SGA ($p = 0.53$), and Apgar score at 1 minute ($p = 0.29$; Tables 1 to 3). There was a significant association between the success of early CPAP with the use of surfactant ($p = 0.001$), mild X-ray findings ($p = 0.007$), pulmonary hemorrhage,

Table 2: Association between maternal risk factor and outcome of early CPAP use

	CPAP prognosis				
	Failure n = 38		*Success n = 65*		
	No	*%*	*No*	*%*	*p-value*
Mode of delivery					
CS	29	73.7	57	89.2	0.113
NVD	9	26.3	8	10.8	
Small for gestational age					
Yes	5	13.2	6	9.2	0.534
No	33	86.8	59	90.8	
Maternal history hypertension					
Yes	11	28.9	25	38.5	0.329
No	27	71.1	40	61.5	
DM					
Yes	6	15.8	7	10.8	0.459
No	32	84.2	58	89.2	
Preeclampsia					
Yes	3	7.9	2	3.1	0.272
No	35	92.1	63	96.9	
Use of antenatal steroid					
Yes	23	60.5	61	93.8	0.0001*
No	15	39.5	4	6.2	
Prolong rupture of membrane >18 hours					
Yes	15	39.5	12	18.5	0.019 *
No	23	60.5	53	81.5	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at <0.05 level

Table 3: Association between Apgar score at 1 and 5 minutes and outcome of early CPAP

	CPAP prognosis				
	Failure n = 38		*Success n = 65*		
	No	*%*	*No*	*%*	*p-value*
Apgar score at 1 minute					
Poor (<7)	37	97.4	60	92.3	0.290
Good (≥7)	1	2.6	5	7.7	
Apgar score at 5 minutes					
Poor (<7)	**7**	**18.4**	**3**	**4.6**	**0.022***
Good (≥7)	31	81.6	62	95.4	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at <0.05 level

sepsis ($p = 0.027$), and being discharged well ($p = 0.0001$). There was no significant association between pneumothorax, BPD, referral, and success of early CPAP (Table 4).

Discussion

Our understanding of the optimum, early application of CPAP in the respiratory management of preterm infants is still developing.[26] In our cohort, 103 (83.7%) were treated with early CPAP. The enthusiasm for initial CPAP therapy is often tempered by concerns about the

Table 4: Association between diagnosis, treatment and outcome of early CPAP use

	CPAP prognosis				
	Failure n = 38		*Success n = 65*		
	No	*%*	*No*	*%*	*p-value*
Use of surfactant					
Yes	**13**	**34.2**	**5**	**7.7**	**0.001***
No	25	65.8	60	92.3	
X-ray finding					
Mild	**26**	**68.4**	**60**	**92.3**	**0.007***
Moderate	2	5.3	1	1.5	
Severe	10	26.3	4	6.2	
Pneumothorax					
Yes	3	7.9	2	3.1	0.272
No	35	92.1	63	96.9	
Pulmonary hemorrhage					
Yes	**16**	**42.1**	**–**	**–**	**0.0001***
No	22	57.9	65	100.0	
Sepsis					
Yes	**16**	**42.1**	**14**	**21.5**	**0.027***
No	22	57.9	51	78.5	
Bronchopulmonary dysplasia					
Yes	1	2.6	1	1.5	0.698
No	37	97.4	64	98.5	
Referral					
Yes	4	10.5	17	26.2	0.057
No	34	89.5	48	73.8	
Outcome					
Improved and discharged well	**11**	**28.9**	**65**	**100.0**	**0.0001***
Dead	27	71.1	–	–	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at <0.05 level

possible consequences of delays in surfactant administration and loss of efficacy of this relatively expensive treatment modality. These findings resemble those reported by Rehman et al. ($p < 0.00001$),[27] but not those of Celik et al.[19] who did not detect this association ($p = 0.118$). These differences could be related to differences in GA in the two cohorts. Celik and coworkers had studied a less mature cohort with a GA <32 weeks.[19] The average BW in our cohort resembled that of Rehman et al.[27] but not with the patients enrolled by Pillai and colleagues, who did not find an association.[28]

In our study, there was a significant association between the use of antenatal steroids and the success of early CPAP. These data agree with those reported by Tavares et al.[29] and Arora et al.[30] Similarly, there was a strong association between PROM and the need for early CPAP, which was consistent with the observations of Pillai and coworkers.[28] We did not find any relationship between Apgar scores at 1 minute and the use of early CPAP. Contrary to the findings noted by Celik et al.[19] our outcomes were better when the 5-minute Apgar scores were higher. There might have been some differences in delivery room resuscitation care.

Similar to the reports of Vieira et al.[31] and Tavares et al.[29] infants treated with early CPAP were less likely to need surfactant therapy, Similarly, more infants treated with early CPAP showed milder radiographic findings of RDS. These findings could indicate that early initiation of CPAP prevented the progression of RDS, but it is also possible that those who had milder respiratory disease were more likely to remain stable with timely institution of CPAP and did not need surfactant and/or MV. These findings resemble those reported by the groups led by both Rehman et al. and Pillai et al.[27,28]

The high incidence of pulmonary hemorrhage in our group likely indicated a higher severity of RDS in our cohort. Other possibilities, such as the protocol for surfactant administration, and the MV settings, could also have played a role and need to be reviewed. Similar to the findings of Boix et al.[32] fewer infants who received early CPAP had a pulmonary hemorrhage. Sepsis and pneumonia also affected the efficacy of early CPAP. These findings are consistent with those reported by the groups led by Koti et al.[33] and Pillai et al.[28] We had a high mortality rate in infants with sepsis. The incidence of BPD was low, but we did not have any infants born prior to 26 weeks gestation who would have been at higher risk of developing chronic lung changes.

In our cohort, preterm infants who were born ≤32 weeks and were treated with early CPAP, (73.8%) improved and were discharged with good outcomes. There was a significant association between improvement and decreased mortality with early CPAP use and these data are in agreement with the teams led by Arora et al.[30] and Hameed et al.[17] who work on the same campus. However, Celik et al.[19] did not find a similar reduction in mortality.

We need more studies in larger cohorts to determine whether our findings will stay consistent in those settings. There is a need for authentic systems for risk assessment with home deliveries, documentation of delays in patient referral, frequencies of hospital readmissions, and access to outpatient care after discharge or in other hospitals. In our conflict-affected regions, the availability of supportive treatment modalities such as blood transfusions in infants with severe anemia of prematurity may also be important.

In a previous report, we have described how access to medical facilities can affect infant outcomes in war zones. Adverse security situations and difficulties in transportation can be important limiting factors. Difficulties in reaching the hospital in a timely fashion, blockage of roads, disruption of infrastructure, and personal constraints can prevent families from seeking medical attention in a timely fashion.[34] The constraints that prevent families from transporting a sick infant to a medical facility also affect the healthcare workers. It is difficult to imagine even after reaching a medical facility, how disheartening it can be to find out that the needed healthcare workers could not make it to the hospital on that day or might never make it. Medical supplies might also be inadequate in quantity or quality, and limitations in the skills of available healthcare providers can be important limiting factors. Some infants may have to be delivered at home by untrained personnel or receive only minimal birthing care in hospitals.

Morbidity and mortality are not only related to the direct effect of an armed conflict but also diminishing medical resources. Reduction of neonatal and child mortality is lagging behind the resolution of armed conflicts. In countries like Iraq, and countries with similar situations such as Yemen, Afghanistan, Mali, and Somalia, neonatal mortalities are among the highest in the world. The differences are appalling when compared to neonatal mortality rates of ≤5 per 1,000 live births in the more peaceful Western countries.[35] In our study, the high mortality and morbidities including the poor outcomes of respiratory support in preterm infants <32 weeks may be related to the maternal-child healthcare system being hampered by many years of long-term conflicts.[36] These data emphasize the need for a global, synergistic quest for solutions.[37]

Conclusion

The study shows that GA >28 and ≤32 weeks, BW ≥1500 gm, use of antenatal steroids, 5-minute Apgar scores >7, and sepsis with absence of PROM >18 hours prior to delivery were associated with significant benefits of early CPAP. The respiratory management of preterm infants with success of early CPAP reduced the need for surfactant and reduced the incidence of complications such as pulmonary hemorrhage. Early CPAP also reduced mortality.

Recommendations

In our conditions, antenatal corticosteroids are advisable for all women at risk of preterm delivery prior to 34 weeks gestation. There is a need to prevent and treat sepsis in a timely fashion and initiate CPAP as early as possible in premature infants with RDS to prevent pulmonary hemorrhage, need for surfactant, and reduce mortality. Further studies are recommended to evaluate the effect of new techniques of surfactant administration such as LISA in infants in high-risk war zones such as Iraq.

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